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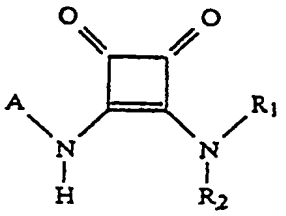
(54) Title: DIAMINOCYCLOBUTENE-3,4-DIONES AS SMOOTH MUSCLE RELAXANTS

(57) Abstract

The compounds of formula (I) wherein R_1 and R_2 are, independently, hydrogen, straight or branched chain alkyl or mono- or bi-cyclic alkyl; A is an N-heterocycle which may be substituted by alkyl, perfluoroalkyl, alkoxy, perfluoroalkoxy, amino, alkylamino, dialkylamino, alkylsulfonamido, alkylcarboxamido, nitro, cyano or carboxyl; or, A is a substituted phenyl group containing one or two substituents selected from cyano, nitro, alkyl, perfluoroalkyl, alkoxy, perfluoroalkoxy, amino, alkylamino, dialkylamino, sulfamyl, alkylsulfonamido, arylcarboxamido, alkylsulfonyl, perfluoroalkylsulfonyl, arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl or carboxyl; or a pharmaceutically acceptable salt thereof, are smooth muscle relaxants.



(I)

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DIAMINOCYCLOBUTENE-3, 4-DIONES AS SMOOTH MUSCLE RELAXANTS

Background of Invention

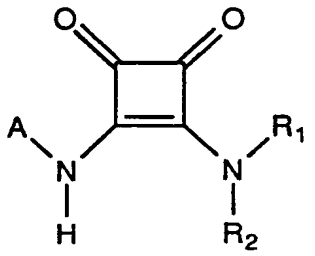
The present invention relates to novel 1, 2-diamino derivatives of cyclobutene 3-4-diones having pharmacological activity, to a process for their preparation, to pharmaceutical compositions containing them, and to their use in the treatment of disorders associated with smooth muscle contraction; via potassium channel modulation. Such disorders include, but are not limited to: urinary incontinence, hypertension, asthma, premature labor, irritable bowel syndrome, congestive heart failure, angina, and cerebral vascular disease.

Stemp et al. disclose a class of amino substituted cyclobutenedione derivatives of chromans described as having blood pressure lowering activity and bronchodilatory activity in EP-426379-A2. Several series of 1-amino-2-phenylalkylamino-cyclobutene-3,4-diones are reported as H-2 receptor antagonists by Algieri et al. in US Patent 4,390,701. Several related 1-amino-2-phenoxyalkylamino derivatives are disclosed by Nohara et al. in US Patent 4,673,747.

The syntheses of variously substituted 1,2-diamino-cyclobutene-3,4-diones are described in the following publications: Tietze et al., *Chem Ber.* **1991**, *124*, 1215; Tietze et al., *Bioconjugate Chem.* **1991**, *2*, 148; Ehrhardt et al., *Chem. Ber.* **1977**, *110*, 2506, and Neuse et al., *Liebigs Ann. Chem.* **1973**, 619. For example, Neuse et al. discloses 1-phenylamino-2-dimethylamino-cyclobut-1-ene-3,4-dione. The compounds of the present invention differ from the Neuse et al. compound in that they are substituted on the phenylamino group and they are useful as smooth muscle relaxants.

Description of The Invention

Accordingly, the present invention discloses compounds represented by the formula (I):

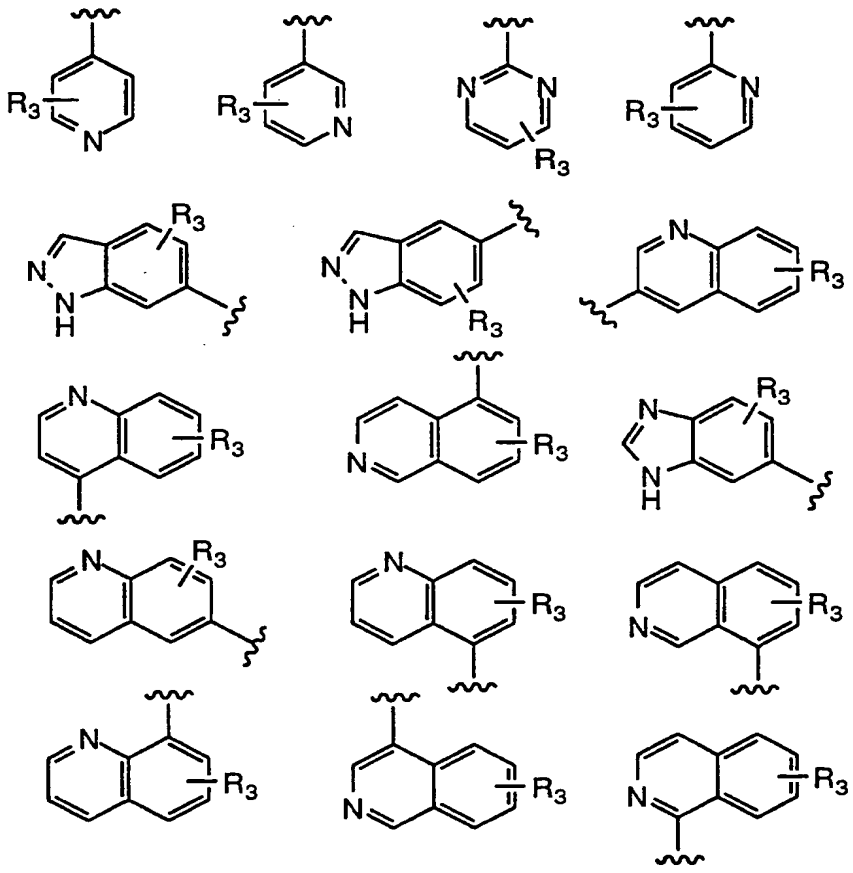


(I)

wherein:

R_1 and R_2 are, independent from each other, hydrogen, C_{1-10} straight chain alkyl, C_{1-10} branched alkyl , or C_{3-10} cyclic or bicyclic alkyl;

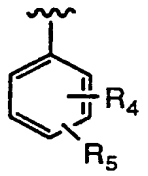
A is selected from the group consisting of:



wherein:

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, C_{1-6} alkylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, nitro, cyano, carboxyl;

or, A is a substituted phenyl group of the following formula:



wherein:

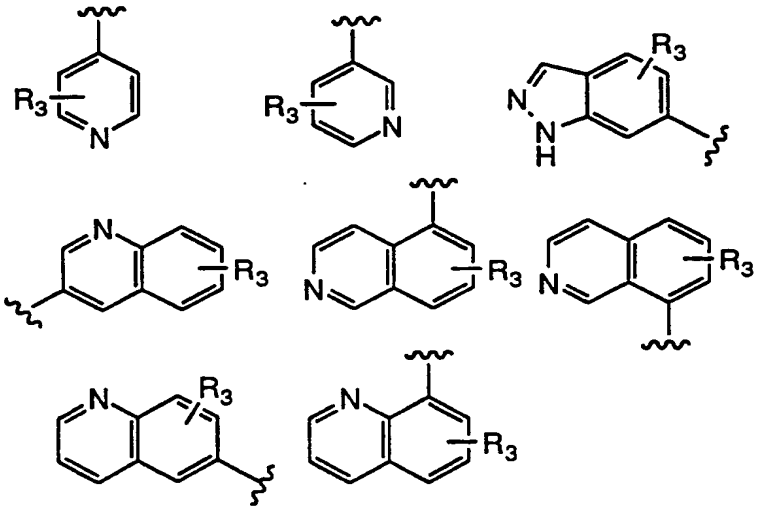
R_4 and R_5, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, sulfamyl, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, arylcarboxamido containing 7 to 13 carbon atoms, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen, with the proviso that R_4 and R_5 cannot be hydrogen simultaneously;

or a pharmaceutically acceptable salt thereof.

A preferred aspect of this invention includes compounds of formula (I) wherein:

R_1 and R_2 are as stated above;

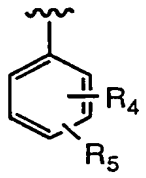
A is selected from the following:



wherein:

R3 is as stated above;

or, A is a substituted phenyl group of the following formula:



wherein:

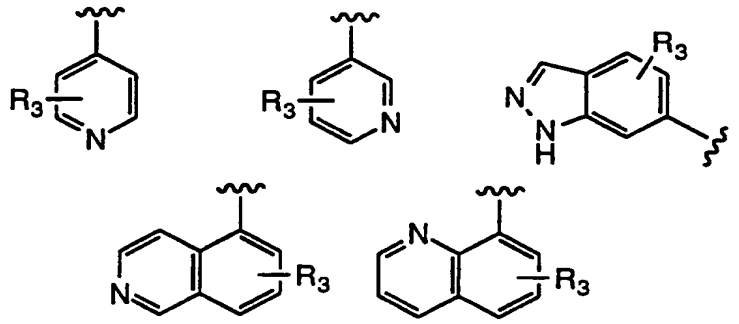
R4 and R5, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl,. carboxyl or hydrogen, with the proviso that R4 and R5 cannot be hydrogen simultaneously;

or a pharmaceutically acceptable salt thereof.

The most preferred aspect of this invention includes compounds of formula (I) wherein:

R1 and R2 are as stated above;

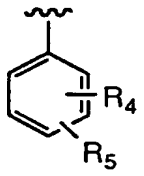
A is selected from the following:



wherein:

R3 is as stated above;

or, A is a substituted phenyl group of the following formula:



wherein:

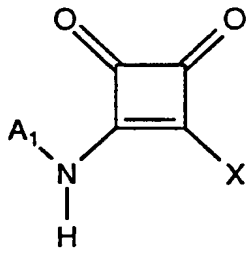
R4 and R5, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen, with the proviso that R4 and R5 cannot both be hydrogen simultaneously;

or a pharmaceutically acceptable salt thereof.

It is understood that the definition of the compounds of formula (I), when R_1, R_2, R_3, R_4. or R_5 contain asymmetric carbons, encompass all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques. The compounds of this invention, throughout this specification, are equivalently name as 3,4-diones or 1,2-diones. The pharmaceutically acceptable salts of the basic compounds of this invention are those

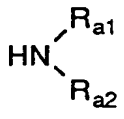
derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids. Where R3, R4, or R5 is a carboxyl group, salts of the compounds of this invention may be formed with bases such as alkali metals (Na, K, Li) or the alkaline earth metals (Ca or Mg).

The present invention also provides a process for the preparation of a compound of formula (I). More particularly, the compounds of formula (I) may be prepared by reacting a compound of formula (IIa):



(IIa)

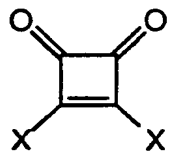
wherein X is a leaving group, for example, methoxy, ethoxy, isopropoxy, halogen or a similar leaving group and A_1 is A, as defined hereinbefore or a group of atoms convertible thereto, with a compound of formula (IV):



(IV)

wherein R_{a1} and R_{a2} are R_1 and R_2, respectively, as defined hereinbefore or a group of atoms convertible thereto and, where appropriate, converting A_1 into A or converting R_{a1} into R_1 or converting R_{a2} into R_2 and, where desired, converting a compound having formula (I) into a pharmaceutically acceptable salt thereof or converting a salt of a compound having formula (I) into a compound having formula (I).

The compounds having formula (IIa) may be prepared by reaction of a compound having (II):



(II)

where X is as defined above with a compound having the formula (III):

$$A_1 — NH_2 \quad \text{(III)}$$

wherein A_1 is as defined above.

The reactions mentioned above may be carried out in a solvent such as methanol or ethanol at elevated temperatures.

As mentioned previously, the compounds of formula (I) and their pharmaceutically acceptable salts have been found to relax smooth muscle. They are therefore useful in the treatment of disorders associated with smooth muscle contraction, disorders involving excessive smooth muscle contraction of the urinary tract (such as incontinence), or of the gastro-intestinal tract (such as irritable bowel syndrome), asthma, and hair loss. Furthermore, the compounds of formula (I) are active as potassium channel activators which render them useful for treatment of peripheral vascular disease, hypertension, congestive heart failure, stroke, anxiety, cerebral anoxia and other neurodegenerative disorders.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example, parenteral administration for patients suffering from heart failure.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention and preferably from 2 to 50 mg. Still further preferred unit dosage forms contain 5 to 25 mg of a compound of the present invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg/kg or preferably at a dose range of 0.1 to 10 mg/kg. Such compositions may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent and the like. They are formulated in conventional manner, for example, in a manner similar to that used for known antihypertensive agents, diuretics and β-blocking agents.

The present invention further provides a compound of the invention for use as an active therapeutic substance. Compounds of formula (I) are of particular use in the induction of smooth muscle relaxation.

The present invention further provides a method of treating smooth muscle disorders in mammals including man, which comprises administering to the afflicted mammal an effective amount of a compound or a pharmaceutical composition of the invention.

The following examples are presented to illustrate rather than limit the methods for production of representative compounds of the invention.

Example 1

3-(Pyridin-4-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(pyridin-4-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100 mL) was added a suspension of 4-aminopyridine (2.77g, 29.4 mmol) in ethanol (50 mL). The reaction mixture was refluxed for 4 hours then concentrated to give crude product. Chromatography (EtOAc) afforded 0.632 g (10%) of a white solid: mp 120-125 °C.

Step 2) Preparation of 3-(pyridin-4-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.332 g, 1.52 mmol) in acetonitrile (30 mL) was added 2-amino-3,3-dimethylbutane (0.200 ml, 1.52 mmol). A precipitate formed while stirring overnight. The crude reaction mixture was vacuum filtered and the precipitate was dried in vacuo to yield 0.328 g (79%) of a pale yellow solid: mp 255-257 °C; ^{1}H NMR (DMSO-d_6): δ 9.80 (s, 1H), 8.42 (dd, 2H), 7.72 (d, 1H), 7.45 (dd, 2H), 3.96-4.00 (m, 1H), 1.18 (s, 3H), 0.91 (s, 9H). IR (KBr): 3200, 1800, 1675, 1600 cm^{-1}; MS (m/z) 274 (MH^+).

Elemental analysis for $C_{15}H_{19}N_3O_2$

Calc'd: C, 65.91; H, 7.01; N, 15.37

Found: C, 65.91; H, 6.96; N, 15.22

Example 2

(Exo)-3-(bicyclo[2.2.1]hept-2-ylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione

To the product of Example 1, Step 1 (0.332 g, 1.52 mmol) in acetonitrile (30 mL) was added (±) exo-2-aminonorbornane (0.180 mL, 1.52 mmol). A precipitate forms while stirring overnight. The reaction mixture was vacuum filtered and the precipitate was dried in vacuo to yield 0.350g (81%) of a pale yellow solid: mp 268-270°C (dec); ^{1}H NMR (DMSO-d_6): δ 9.70 (s, 1H), 8.40 (d, 2H), 7.74 (d, 1H), 7.42 (d, 2H), 3.90-3.95 (m, 1H), 2.23-2.31 (m, 2H), 1.78-1.84 (m, 1H), 1.09-1.54 (m, 7H). IR (KBr): 3200, 1795, 1670, 1600 cm^{-1}; MS (m/z) 283 (M^+).

Elemental analysis for $C_{16}H_{17}N_3O_2$

Calc'd: C, 67.83; H, 6.05; N, 14.83

Found: C, 67.48; H, 6.03; N, 14.66

Example 3

3-(Pyridin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(pyridin-3-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100mL) was added a suspension of 3-aminopyridine (2.77g, 29.4 mmol) in ethanol (50 mL). The mixture was heated at reflux for 18 hours, then concentrated. Chromatography (4:1 EtOAc/hexane) afforded 3.15 g (49%) of a white solid: mp 140-145 °C.

Step 2) Preparation of 3-(pyridin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.328 g, 1.50 mmol) in acetonitrile (30 mL) was added 2-amino-3,3-dimethylbutane (0.200 mL, 1.52 mmol). A precipitate forms while stirring overnight. The crude reaction mixture was vacuum filtered and the precipitate was dried in vacuo to yield 0.27 g (66%) of a white solid: mp 243-245°C; ^{1}H NMR (DMSO-d_6): δ 9.67 (s, 1H), 8.58 (d, 1H),7.98 (d, 1H), 7.66 (d, 1H), 7.38 (m, 1H), 3.96-4.00 (m, 1H), 1.18 (s, 3H), 0.95 (s, 9H) ; IR (KBr): 3200, 1800, 1665, 1600 cm^{-1}. MS (m/z) 273 (M^+).

Elemental analysis for $C_{15}H_{19}N_3O_2$

Calc'd: C, 65.91; H, 7.01; N, 15.37

Found: C, 65.92; H, 6.95; N, 15.24

Example 4

3-(2-Methylethylamino)-4-(pyridin-3-ylamino)(cyclobut-3-ene-1,2-dione

To the product from Example 3, Step 1 (0.180 g, 0.825 mmol) in acetonitrile (100 mL) was added isopropylamine (20 mL, 235 mmol). The reaction was stirred at room temperature overnight, then concentrated. Trituration with ethylacetate/diethylether afforded 0.135 g (71%) of a white solid: mp 258-260 °C; ^{1}H NMR (DMSO-d_6): δ 9.62 (br s, 1H), 8.55 (s, 1H), 8.22 (d, 1H), 7.94 (br d, 1H), 7.73 (br s, 1H), 7.36 (dd, 1H), 4.20 (br m, 1H), 1.25 (d, 6H). IR (KBr): 3200, 1800, 1660, 1610 cm^{-1}; MS (m/z) 231(M^+).

Elemental analysis for $C_{12}H_{13}N_3O_2$

Calc'd: C, 62.32; H, 5.66; N, 18.17

Found: C, 62.86; H, 5.79; N, 18.53

Example 5

3-Dimethylamino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione

To the product from Example 3, Step 1 (0.330 g, 1.51 mmol) in acetonitrile (200 mL) was introduced to a stream of dimethylamine gas (15 minutes). The

resultant solution was stirred overnight at room temperature, concentrated, and triturated with dichloromethane/diethylether to afford 0.278g (85%) of an white solid: mp 235-237 °C; ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 8.46 (s, 1H), 8.22 (d, 1H), 7.60 (d, 1H), 7.32 (dd, 1H). IR (KBr): 1790, 1685, 1600 cm^{-1}; MS (m/z) 217 (M^+).

Elemental analysis for $C_{11}H_{11}N_3O_2$

Calc'd: C, 60.82; H, 5.10; N, 19.34

Found: C, 60.71; H, 5.07; N, 19.46

Example 6

3-Amino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione

To the product from Example 3, Step 1 (0.330 g, 1.51 mmol) in acetonitrile (200 mL) was introduced to a stream of ammonia gas until solution became turbid. The resultant mixture was stirred overnight at room temperature. The precipitate was vacuum filtered and dried to afford 0.266g (93%) of a white solid: mp 297 °C(dec); ^{1}H NMR (DMSO-d_6): δ 8.56 (s, 1H), 8.22 (d, 1H), 7.92 (d, 1H), 7.37 (m, 1H). IR (KBr): 3200, 1800, 1670, 1625 cm^{-1}; MS (m/z) 189 (M^+).

Elemental analysis for $C_9H_7N_3O_2$

Calc'd: C, 57.14; H, 3.73; N, 22.21

Found: C, 57.18; H, 3.69; N, 22.10

Example 7

3-Tert-butylamino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione

The product from Example 3, Step 1 (2.60 g, 11.9 mmol) was dissolved in tert-butylamine (50 mL). The solution was refluxed for three hours, cooled, and concentrated in vacuo. Trituration with diethylether afforded 1.05 g (36%) of a white solid: mp 250-252 °C; ^{1}H NMR (DMSO-d_6): δ 8.57 (s, 1H), 8.23 (d, 1H), 7.96 (d, 1H), 7.37 (m, 1H) 1.43 (s,9H). IR (KBr): 1790, 1685, 1600 cm^{-1}; MS (m/z) 245 (M^+).

Elemental analysis for $C_{13}H_{15}N_3O_2$
Calc'd: .C, 63.66; H, 6.16; N, 17.13
Found: C, 63.28; H, 6.22; N, 17.07

Example 8

3-Tert-butylamino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(isoquinolin-5-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100 mL) was added a suspension of 5-aminoisoquinoline (4.24g, 29.4 mmol) in ethanol (50 mL). The mixture was heated to reflux overnight and then filtered to yield 2.30 g (29%) of solid: mp 182(dec) °C.

Step 2) Preparation of 3-Tert-butylamino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione one-eighth hydrate

The above squarate (0.300 g, 1.12 mmol) was dissolved in tert-butylamine (50 mL) and refluxed for three hours. The mixture was cooled, concentrated, and triturated with diethylether to afford 0.120 g (39%) of the title compound as a white solid, one-eighth hydrate: mp 268-270 °C(dec); ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1H), 9.35 (s, 1H), 8.62 (d, 1H), 8.19 (s, 1H), 8.01 (d, 1H), 7.88 (d, 1H), 7.80 (d, 1H), 7.68 (t, 1H), 1.47 (s, 9H). IR (KBr): 3200, 1785, 1670, 1600 cm^{-1}; MS (m/z) 295 (M^+).

Elemental analysis for $C_{17}H_{17}N_3O_2 \cdot 0.125\ (H_2O)$
Calc'd: .C, 68.61; H, 5.84; N, 14.12
Found: C, 68.08; H, 5.78; N, 13.75

Example 9

3-Amino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione

A suspension of the the product from Example 8, Step 1 (0.190 g, 0.700 mmol) in ethanol (3.5 mL) was saturated with ammonia, capped, and heated to 45°C for three hours. The mixture was cooled, concentrated, and triturated with diethylether . Crude product was recrystallized from dimethylformamide/water to give 0.129 g (77%) of the title compound as a pale yellow solid, one-eighth hydrate: mp 215°C; ^{1}H NMR (DMSO-d_6): δ 9.87 (s, 1H), 9.34 (s, 1H), 8.60 (d, 1H), 7.40-8.60 (broad signal, NH2), 8.02 (d, 1H), 7.86 (d, 1H), 7.77 (d, 1H), 7.68 (t, 1H). IR (KBr): 3200, 1800, 1690, 1650 cm^{-1}; MS (m/z) 240(MH$^+$).

Elemental analysis for $C_{13}H_9N_3O_2 \cdot 0.125\ (H_2O)$

Calc'd: C, 64.66; H, 3.86; N, 17.40

Found: C, 64.10; H, 3.74; N, 16.99

Example 10

3-(Quinolin-8-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(quinolin-8-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione

To a solution of 8-aminoquinoline (1.00 g, 6.94 mmol) in ethanol (20 mL) was added 3,4-diethoxy-3-cyclobutene-1,2-dione (1.03 mL, 6.94 mmol) and the resulting mixture was heated to reflux for 24 hours. The mixture was cooled, diluted with ethanol, and filtered. The crude product was triturated with chloroform/hexanes, then purified by chromatography (EtOAc/hexane) to give 1.31 g (70%) of product: ^{1}H NMR (DMSO-d_6) δ 9.75 (br m, 1 H), 8.86 (dd, 1 H), 8.26 (br m, 1H), 8.20 (dd, 1H), 7.57 (m, 2H), 7.53 (dd, 1H), 4.95 (q, 2H), 1.59 (t, 3H).

Step 2) Preparation of 3-(quinolin-8-ylamino)-4-(1,2,2-trimethylpropylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.300 g, 1.12 mmol) in ethanol (5 mL) was added 2-amino-3,3-dimethylbutane (0.18 mL, 1.34 mmol) and the resulting mixture was heated at 45° C overnight, diluted with hexanes, and filtered to give 0.294 g (81%) of a yellow solid: mp 244-245; ^{1}H NMR (DMSO-d$_6$) δ 10.45 (s, 1H), 8.97 (dd, 1H), 8.62 (d, 1H), 8.41 (dd, 1H), 8.29 (dd, 1H), 7.6 (m, 3H), 4.10 (m, 1H), 1.21 (d, 3H), 0.94 (s, 9H). IR (KBr): 3280, 2960, 1790, 1670 cm^{-1}; MS (m/z) 323 (MH$^+$).

Elemental analysis for $C_{19}H_{21}N_3O_2$

Calc'd: C, 70.56; H, 6.54; N, 12.99

Found: C, 70.38; H, 6.51; N, 12.94

Example 11

3-Methylamino-4-(quinolin-8-ylamino)-cyclobut-3-ene-1,2-dione

To the product from Example 10, Step 1 (0.64 g, 2.38 mmol) was added ethanolic methylamine (8.03 M, 13 mL) and the mixture was stirred at 25 °C for 6 hours. Diethyl ether was added, and the resulting solid was filtered and washed with additional ether. Chromatography (EtOAc/hexanes) followed by trituration with dimethylsulfoxide/water afforded 0.398 g (66%) of product as a yellow solid: mp 236-237°C; ^{1}H NMR (DMSO-d$_6$) δ 10.32 (s, 1H), 8.95 (dd, 1H), 8.63 (m, 1H), 8.40 (dd, 1H), 8.26 (d, 1H), 7.68-7.54 (m, 3H), 3.27 (d, 3H). IR (KBr) 3200, 1795, 1610 cm^{-1}; MS (m/z) 253 (M$^+$), 155 (100%).

Elemental analysis for $C_{14}H_{11}N_3O_2$

Calc'd: C, 66.39; H, 4.38; N, 16.59

Found: C, 66.13; H, 4.43; N, 16.48

Example 12

3-Amino-4-(quinolin-8-ylamino)-cyclobut-3-ene-1,2-dione

Ammonia gas was bubbled through a slurry of the product from Example 10, Step 1 (0.640 g, 2.38 mmol) in ethanol (13 mL) at -35 °C. After 6 hours, the mixture was diluted with diethylether and filtered. Chromatography (EtOAc/hexanes) followed by trituration with dimethylsulfoxide/water afforded 0.342 g (60%) of product as a yellow solid, quarter hydrate: mp 263°C (dec); ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 8.95 (dd, 1H), 8.45 (br s, 2H), 8.40 (dd, 1H), 8.28 (dd, 1H), 7.66-7.55 (m, 3H). IR (KBr) 3260, 1800 cm^{-1}; MS (m/z) 239 (M+), 211, 183, 155, 129 (100%).

Elemental analysis for $C_{13}H_9N_3O_2 \cdot 0.25\ (H_2O)$

Calc'd: C, 64.06; H, 3.72; N, 17.24

Found: C, 63.28; H, 3.85; N, 16.99

Example 13

3-(Quinolin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(Quinolin-3-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione

To a solution of 3-aminoquinoline (2.12 g, 14.69 mmol) in ethanol (60 mL) was added 3,4-diethoxy-3-cyclobutene-1,2-dione (2.50 g, 14.69 mmol) and the resulting mixture was heated to reflux for 24 hours. The mixture was cooled, filtered, and the product was washed with diethylether and dried in vacuo to give 3.14 g (80%) of yellow solid which was used without purification: ^{1}H NMR (DMSO-d_6) δ 11.14 (s, 1H), 8.92 (dd, 1H), 8.20 (dd, 1H), 7.90 (m, 2H), 7.63 (m, 2H).

Step 2) Preparation of 3-(Quinolin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.30 g, 1.12 mmol) in ethanol (8 mL) was added 2-amino-3,3-dimethylbutane (0.18 mL, 1.34 mmol) and the resulting mixture was heated at 50° C overnight. The precipitate was filtered, washed with diethylether, and dried in vacuo to afford 0.30 g (83%) of product as a light tan solid: mp 242-246°C; ^{1}H NMR (DMSO-d6) δ 9.93 (s, 1H), 8.90 (d, 1H), 8.38 (br s, 1H), 7.97 (d, 1H), 7.84 (dd, 1H), 7.75-7.55 (m, 2H), 4.00 (m, 1H), 1.20 (d, 3H), 0.94 (s, 9H). IR (KBr) 3160, 2960, 1795, 1650 cm^{-1}; MS (m/z) 324 (MH^+).

Elemental analysis for $C_{19}H_{21}N_3O_2$

Calc'd: C, 70.57; H, 6.55; N, 12.99

Found: C, 70.97; H, 6.41; N, 13.04

Example 14

3-Tert-butylamino-4-(quinolin-3-ylamino)-cyclobut-3-ene-1,2-dione

To the product from Example 13, Step 1 (0.30 g, 1.12 mmol) in ethanol (8 mL) was added tert-butylamine (0.35 mL, 3.36 mmol) and the resulting mixture was heated at 60° C overnight. The mixture was concentrated, and the residue was dissolved in ethylacetate. Addition of hexanes induced precipitation of product which was filtered and triturated with diethylether/hexanes. Filtration and drying afforded 0.28 g (85%) of the title compound as a yellow solid, three -quarter hydrate: mp 257-260°C; ^{1}H NMR (DMSO-d$_6$) d 10.00 (br d, 1H), 8.9 (d, 1H), 8.4 (m, 1H), 8.02 (d, 1H), 7.96 (br d, 1H), 7.86 (dd, 1H), 7.66-7.54 (m, 2H), 1.45 (s, 9H). IR (KBr) 3400, 3200, 2980, 1785, 1680 cm^{-1}; MS (m/z) 296 (MH^+).

Elemental analysis for $C_{17}H_{17}N_3O_2 \cdot 0.75\ (H_2O)$

Calc'd: C, 66.11; H, 6.04; N, 13.61

Found: C, 66.08; H, 5.86; N, 13.36

Example 15

3-(Quinolin-3-ylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione

To the product from Example 13, Step 1 (0.30 g, 1.12 mmol) in ethanol (7 mL) was added tert-amylamine (0.39 mL, 3.35 mmol). After 48 hours of stirring at 45°C, an additional aliquot of amine (0.39 mL) was added. After 3 hours, the mixture was concentrated and the residue was triturated with hexane/diethylether to give 0.328 g (95%) of product as an off white solid, three-quarter hydrate: mp 234-236°C; 1 H NMR (DMSO-d6) δ 10.04 (br s, 1H), 8.9 (d, 1H), 8.4 (d, 1H), 7.95 (d, 1H), 7.86, (m, 2H), 7.6 (m, 2H), 1.78 (q, 2H), 1.40 (s, 6H), 0.89 (t, 3H). IR (KBr) 3370, 3240, 2960, 1785, 1680 cm^{-1}; MS (m/z) 309 (M^+).

Elemental analysis for $C_{18}H_{19}N_3O_2 \cdot 0.75\ (H_2O)$

Calc'd: C, 66.96; H, 6.40; N, 13.01

Found: C, 67.11; H, 6.26; N, 13.05

Example 16

3-(6-Methoxy-quinolin-8-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(6-Methoxy-quinolin-8-ylamino)-4--ethoxy-cyclobut-3-ene-1,2-dione

In a procedure identical to Example 10, Step 1, 8-amino-6-methoxyquinoline (2.00 g, 11.48 mmol) was reacted with 3,4-diethoxy-3-cyclobutene-1,2-dione (1.70 mL, 11.48 mmol) to give 0.99 g (29%) of product: ^1H NMR (DMSO-d_6) δ 10.21 (s, 1H), 8.75 (dd, 1H), 8.29 (dd, 1H), 7.61 (m, 2H), 7.17 (d, 1H), 4.76 (q, 2H), 3.90 (s, 3H), 1.40 (t, 3H).

Step 2) Preparation of 3-(6-Methoxy-quinolin-8-ylamino)-4--(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione

In a procedure identical to Example 10, Step 2, the above squarate (0.25 g, 0.839 mmol) and 2-amino-3,3-dimethylbutane (0.13 mL, 1.01 mmol) were reacted to give 0.21 g (71%) of title compound as an off-white solid: mp 243-245°C; ^{1}H NMR (DMSO-d_6) δ 10.43 (br s, 1H), 8.78 (dd, 1H), 8.64 (d, 1H), 8.28 (dd, 1H), 8.13 (d, 1H), 7.56 (dd, 1H), 7.02 (d, 1H), 4.11 (m, 1H), 3.88 (s, 3H), 1.20 (d, 3H), 0.94 (s, 9H). IR (KBr) 3400, 3220, 2950, 1780 cm^{-1}; MS (m/z) 353 (M^+).

Elemental analysis for $C_{20}H_{23}N_3O_3$

Calc'd: C, 67.96; H, 6.55; N, 11.88

Found: C, 67.72; H, 6.56; N, 11.74

Example 17

3-(6-Methoxy-quinolin-8-ylamino)-4-methylamino-cyclobut-3-ene-1,2-dione

The product from Example 16, Step 1 (0.25 g, 0.839 mmol) was added to 8 N ethanolic methylamine (7 mL). The resulting mixture was stirred for 4 hours and filtered. The solid was recrystallized from dimethylsulfoxide/water to give 0.12 g (50%) of product as a yellow solid: mp >275°C; ^{1}H NMR (DMSO-d_6) δ 10.29 (br s, 1H), 8.75 (dd, 1H), 8.68 (br q, 1H), 8.27 (dd, 1H), 8.10 (d, 1H), 7.55 (m, 1H), 7.00 (d, 1H), 3.88 (s, 3H), 3.26 (d, 3H). IR (KBr) 3240, 1795 cm^{-1}; MS (m/z) 283 (M^+), 185 (100%).

Elemental analysis for $C_{15}H_{13}N_3O_3$

Calc'd: C, 63.59; H, 4.62; N, 14.83

Found: C, 63.30; H, 4.58; N, 14.70

Example 18

3-Tert-butylamino-4-(quinolin-6-ylamino)-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100 mL) was added a suspension of 6-aminoquinoline (4.24 g, 29.4

mmol) in ethanol (50 mL). The mixture was heated at reflux for 18 hours, cooled, and vacuum filtered to afford 6.64 g (84%) of crude product (mp: 185-187, dec) which was used without further purification. An aliquot (3.00 g, 11.2 mmol) was dissolved in tert-butylamine (50 mL). The solution was refluxed for three hours, cooled, and concentrated. The residue was recrystallized twice from ethanol then triturated with diethylether to give 1.05g (31%) of the title compound as a pale yellow solid, one-quarter hydrate: mp 234-236 °C; ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 8.76 (d, 1H), 8.24 (d, 1H), 8.01 (d, 1H), 7.98 (s, 1H), 7.97 (d, 1H), 7.88 (d, 1H), 7.48 (m, 1H), 1.45 (s, 9H). IR (KBr): 1780, 1665, 1610 cm^{-1}; MS (m/z) 295 (M^+).

Elemental analysis for $C_{17}H_{17}N_3O_2 \cdot 0.25\ (H_2O)$

Calc'd: C, 68.10; H, 5.88; N, 14.01

Found: C, 67.63; H, 5.92; N, 13.96

Example 19

3-Tert-butylamino-4-(1H-indazol-6-ylamino)-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (4.51g, 26.5 mmol) in absolute ethanol (100 mL) was added a suspension of 6-aminoindazole (3.53g, 29.4 mmol) in ethanol (50 mL). The mixture was refluxed for 18 hours, cooled, and vacuum filtered to afford 3.60 g (53%) of crude product which was used without further purification. An aliquot (2.00 g, 7.77 mmol) was dissolved in tert-butylamine (50 mL) and the resulting mixture was refluxed for three hours, cooled, and concentrated. The crude product was recrystallized from ethanol/water to give 0.45 g (19%) of the title compound as a white solid, dihydrate: mp 183-185 °C; ^{1}H NMR (DMSO-d_6): δ 13.00 (s, 1H), 9.74 (s, 1H), 7.97 (s, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.70 (d, 1H), 7.05 (d, 1H), 1.44 (s, 9H). IR (KBr): 3200, 1790, 1655, 1600 cm^{-1}; MS (m/z) 284 (M^+).

Elemental analysis for $C_{15}H_{16}N_4O_2 \cdot 2\ (H_2O)$

Calc'd: C, 56.24; H, 6.29; N, 17.49

Found: C, 56.06; H, 6.29; N, 17.43

Example 20

3-(Isoquinolin-5-ylamino)-4-methylamino-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100 mL) was added a suspension of 5-aminoisoquinoline (4.24 g, 29.4 mmol) in ethanol (50 mL). The mixture was heated at reflux for 18 hours, cooled, and vacuum filtered to afford 2.30 g (29%) of crude product (mp: 182, dec) which was used without further purification. To an aliquot (0.335 g, 1.25 mmol) of the squarate in ethanol (1.5 mL) was added 33% methylamine in ethanol (1.4 mL). The mixture was heated to 40°C for 15 minutes, cooled, and concentrated. Trituration with diethylether afforded crude product which was crystallized from a minimal amount of methanol to give 0.149 g (47%) of an pale yellow solid: mp 245-250 °C (dec); ^{1}H NMR (DMSO-d_6): δ 9.79 (s, 1H), 9.33 (s, 1H), 8.60 (d, 1H), 7.99 (d, 1H), 7.86 (d, 1H), 7.76 (br d, 1H), 7.66 (t, 1H), 7.76 (br s, 1H). IR (KBr): 3200, 1800, 1680, 1605 cm^{-1}; MS (m/z) 253 (M^+).

Elemental analysis for $C_{14}H_{11}N_3O_2$

Calc'd: C, 66.40; H, 4.38; N, 16.59

Found: C, 66.06; H, 4.35; N, 16.32

Example 21

4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylaminol-benzonitrile

Step 1) Preparation of 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile

4-Aminobenzonitrile (3.47g, 29.4 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00g, 29.4 mmol) in absolute ethanol (100 mL). The mixture was heated at reflux overnight. The mixture was cooled, and the resulting yellow precipitate was collected by vacuum filtration. Yield: 2.60 g (37%): mp 218-222 °C.

Step 2) Preparation of 4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzonitrile

To the above squarate (1.00 g, 4.13 mmol) in acetonitrile (250 mL) was added 2-amino-3,3-dimethylbutane (0.600 mL, 4.48 mmol). A precipitate forms while stirring overnight. The crude reaction mixture is vacuum filtered. The solid is triturated with diethylether to afford 0.620 g (50%) of product as a yellow solid: mp 241-243°C ; ^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1H), 7.78 (d, 2H), 7.72 (d, 1H), 7.60 (d, 2H), 3.95-4.00 (m, 1H), 1.18 (d, 3H), 0.91 (s, 9H). IR (KBr): 3200, 1790, 1660, 1600 cm^{-1}; MS (m/z) 297 (M^+).

Elemental analysis for $C_{17}H_{19}N_3O_2$

Calc'd: C, 68.67; H, 6.44; N, 14.13

Found: C, 68.63; H, 6.15; N, 14.30

Example 22

(Exo)-4-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile

To the product of Example 21, Step 1 (0.368 g, 1.52 mmol) in acetonitrile (30 mL) was added (+)exo-2-aminonorbornane (0.180 mL, 1.52 mmol). A precipitate forms while stirring overnight. The crude reaction mixture was vacuum filtered and triturated with diethylether to afford 0.370 g (79%) of a yellow solid: mp 288-290°C ; ^{1}H NMR (DMSO-d_6): δ 9.79 (s, 1H), 7.78 (d, 2H), 7.76 (m, 1H), 7.58 (d, 2H), 3.90-3.98 (m, 1H), 2.22-2.34 (m, 2H), 1.76-1.86 (m, 1H), 1.08-1.56 (m, 7H). IR (KBr): 2220, 1790, 1650, 1600 cm^{-1}; MS (m/z) 307 (M^+).

Elemental analysis for $C_{18}H_{17}N_3O_2$

Calc'd: C, 70.34; H, 5.57; N, 13.67

Found: C, 70.17; H, 5.50; N, 13.96

Example 23

4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylaminol-benzenesulfonamide

To a slurry of sulfanilamide (1.72 g, 10.0 mmol) in ethanol (10 mL) was added 3,4-diethoxy-3-cyclobutene-1,2-dione (2.43 g, 14.3 mmol). The reaction was heated at reflux overnight, cooled, and a yellow precipitate was collected by vacuum filtration. Yield: 2.60 g (98%): mp 210-212 °C.

To the above squarate (0.750 g, 2.84 mmol) in ethanol (10 mL) was added 2-amino-3,3-dimethylbutane (0.380 mL, 2.84 mmol). The mixture was heated to reflux overnight then concentrated. The residue was dissolved in acetone/ethylacetate (1:1) and filtered through a plug of silica gel to afford 0.200 g (20%) of the title compound as a white solid, hemi-hydrate: mp 233-235°C ; ^{1}H NMR (DMSO-d_6): δ 9.87 (s, 1H), 7.79 (d, 2H), 7.75 (d, 1H), 7.58 (d, 2H), 7.25 (s, 2H), 4.00 (m, 1H), 1.18 (d, 3H), 0.92 (s, 9H). IR (KBr): 1790, 1670, 1600 cm^{-1}; MS (m/z) 351 (M^+).

Elemental analysis for $C_{16}H_{21}N_3O_4S \cdot 1/2\ H2O$

Calc'd: C, 53.32; H, 6.15; N, 11.66

Found: C, 52.89; H, 5.81; N, 11.42

Example 24

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylaminol-3-ethyl-benzonitrile

Step 1) Preparation of 4-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-3-ethylbenzonitrile

4-Amino-3-ethylbenzonitrile (0.86 g, 5.88 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (1.0 g, 5.88 mmol) in acetonitrile (2 mL) was heated in an oil bath at 110°C for 21 h. 3,4-diethoxy-3-cyclobutene-1,2-dione (0.5 g, 2.9 mmol) was added to the reaction mixture and the temperature of the oil bath increased to 150°C. After 48 h the reaction mixture was cooled to room temperature, then diluted with

ethyl acetate and filtered. The filtrate was concentrated and the resulting solid was taken up in ethyl acetate (5 mL) and sonicated. Filtration gave 0.54 g (34%) of a light brown solid: ^{1}H NMR (DMSO-d_6): δ 10.56 (br s, 1H), 7.70 (br s overlapping a doublet at δ 7.69, 2H), 7.30 (d, 1H), 4.71 (q, 2H), 2.74 (q, 2H), 1.37 (t, 3H), 1.15 (t, 3H).

Step 2) (+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile

4-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-3-ethyl-benzonitrile (1.26 g, 4.66 mmol) and a solution of (R)-1,2,2-trimethylpropylamine (9.3 mmol) in ethanol (58 mL) were stirred at room temperature for 24 h. The resulting yellow solution was concentrated to a yellow oil, which was dissolved in acetonitrile (20 mL) and stirred at room temperature. The resulting yellow solid was filtered and rinsed with ethyl acetate to yield 0.79 g (52%) of an off-white solid: mp 235-237°C; $[\alpha]_D^{25} = +68.20°$ (DMSO, c 0.0072); ^{1}H NMR (DMSO-d_6): δ 8.04 (br s, 1H), 8.04 (d, 1H), 7.69-7.57 (m, 3H), 4.05 (m, 1H), 2.71 (q, 2H), 1.27-1.16 (overlapping doublet and triplet, 6H), 0.91 (s, 9H). IR (KBr): 3278, 2959, 2222, 1793, 1674, 1598, 1576, 1522 cm^{-1}; MS (m/z) 325 (M^+).

Elemental analysis for $C_{19}H_{23}N_3O_2$

Calc'd: C, 70.13; H, 7.12; N, 12.91
Found: C, 69.82; H, 7.17; N, 12.99

Example 25

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-methoxy-benzonitrile

Step 1) Preparation of 4-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-3-methoxybenzonitrile

To a cooled solution of 3-methoxybenzonitrile (10 g, 75 mmol) in acetic anhydride (150 ml) was added 70% nitric acid (60 mL) at a rate that kept the reaction mixture below 50°C. After 1 h the reaction mixture was poured onto ice (400 cc) and

extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried (Na_2SO_4). Concentration under reduced pressure and chromatography with ethyl acetate/hexanes gave 2.69 g (20%) of 3-methoxy-4-nitrobenzonitrile: ^1H NMR (DMSO-d_6): δ 8.04 (d, 1H), 7.93 (d, 1H), 7.61 (dd, 1H), 3.97 (s, 3H). 3-Methoxy-4-nitrobenzonitrile (2.6 g, 14.6 mmol) was suspended in ethanol(100 mL) and added to a mixture of 5% platinum on carbon (250 mg) in ethanol (150 mL). The reaction mixture was stirred under a hydrogen gas atmosphere. After 24 h the reaction was filtered, concentrated, and chromatographed (ethyl acetate/hexanes, 25/75) to yield 1.3 g (60%) of 4-amino-3-methoxybenzonitrile: ^1H NMR (DMSO-d_6): δ 7.1 (m, 2H), 6.65 (d, 1H), 5.77 (br s, 2H), 3.79 (s, 3H). 4-Amino-3-methoxybenzonitrile (1.3 g, 8.77 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (1.5 g, 8.82 mmol) in ethanol (50 mL) was heated in an oil bath at 110-115°C for 3 days. The reaction mixture was filtered hot, and the filtrate was reduced to half its volume. Filtration gave 0.58 g (24%) of a yellow solid: mp 159-161°C; ^1H NMR (DMSO-d_6): δ 10.42 (br s, 1H), 7.54 (d, 1H), 7.44 (dd, 1H), 7.39 (d, 1H), 4.70 (q, 2H), 3.86 (s, 3H), 1.36 (t, 3H). IR (KBr): 3413, 3026, 2650, 2576, 2439, 1719, 1630, 1548 cm^{-1}; MS (m/z) 272 (M^+).

Elemental analysis for $C_{14}H_{12}N_2O4 \cdot 0.2\ H_2O$

Calc'd: C, 60.95; H, 4.53; N, 10.15

Found: C, 60.96; H, 4.32; N, 10.23

Step 2) (+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-methoxy-benzonitrile

4-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-3-methoxy-benzonitrile (0.58 g, 2.1 mmol) and a solution of (R)-1,2,2-trimethylpropylamine (4.2 mmol) in ethanol (21 mL) were stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated to a foam, which was dissolved in acetonitrile (10 mL). Upon standing at room temperature fluffy pale yellow needles formed. This was filtered and rinsed sparingly with acetonitrile to yield 0.46 g (67%) of a pale yellow needles: mp 273-277°C (dec); $[\alpha]_D^{25} = +62.86°$ (DMSO, c 0.010); ^1H NMR (DMSO-d_6): δ 9.49 (br s, 1H), 8.31 (d, 1H), 7.99 (d, 1H), 7.50 (d, 1H), 7.43 (dd, 1H), 4.03 (m, 1H), 3.97 (s, 3H), 1.18 (d, 3H), 0.90 (s, 9H). MS (m/z) 327 (M^+).

Elemental analysis for $C_{18}H_{21}N_3O_3$

Calc'd: C, 66.04; H, 6.47; N, 12.84
Found: C, 66.02; H, 6.39; N, 12.61

The smooth muscle relaxing activity of the compounds of this invention was established in accordance with standard pharmaceutically accepted test procedures in representative compounds as follows:

Sprague-Dawley rats (150-200 g) are rendered unconscious by CO_2 asphyxiation and then euthanized by cervical dislocation. The bladder is removed into warm (37 deg.C) physiological salt solution (PSS) of the following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 4.7; H_2O, 1.2; $NaHCO_3$, 24.9; KH_2PO_4, 1.2; glucose, 11.1; EDTA, 0.023; gassed with 95% O_2; 2/5% CO_2; pH 7.4. The bladder is opened and then cut into strips 1-2 mm in width and 7-10 mm in length. The strips are subsequently suspended in a 10 mL tissue bath under an initial resting tension of 1.5 g. The strips are held in place by two surgical clips one of which is attached to a fixed hook while the other is attached to an isometric force transducer. The preparations, which usually exhibit small spontaneous contractions, are allowed to recover for a period of 1 hour prior to a challenge with 0.1 uM carbachol. The carbachol is then washed out and the tissue allowed to relax to its resting level of activity. Following one further 30 minute period of recovery, an additional 15 mM KCl are introduced into the tissue bath. This increase in KCl concentration results in a large increase in the amplitude of spontaneous contractions (and initiation of contractions in previously quiescent strips) superimposed upon a small increase in basal tone. Following stabilization of this enhanced level of contractile activity, incremental increases in the concentration of test compound or vehicle are introduced into the tissue bath. Contractile activity is measured for each compound or vehicle concentration during the last minute of a 30 minute challenge.

The isometric force developed by the bladder strips is measured using a concentration required to elicit 50% inhibition of pre-drug contractile activity (IC_{50} concentration) is calculated from this concentration-response curve. The maximum percentage inhibition of contractile activity evoked by a test compound is also recorded for concentrations of test compound less than or equal to 30 μM.

The results of this study are shown in Table I.

Table I

Inhibition of Contractions in Isolated Rat Bladder Strips

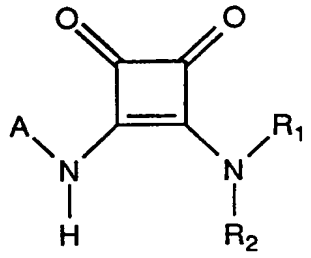
Compound	no. of animals	IC_{50}	Inhibition of Force (%) at (x) μM
Example 1	6	1.36 μM	-
Example 2	2	15.85 μM	-
Example 3	3	1.95 μM	-
Example 6	2	-	31% (30 μM)
Example 7	2	2.8 μM	-
Example 8	4	1.84 μM	-
Example 9	4	-	43% (30 μM)
Example 10	4	8.0 μM	-
Example 14	4	-	51% (30 μM)
Example 19	4	6.34 μM	-
Example 21	2	0.52 μM	-
Example 24	2	0.021 μM	
Example 25	2	0.29 μM	

Hence, the compounds of this invention have a pronounced effect on smooth muscle contractility and are useful in the treatment of urinary incontinence, irritable bladder and bowel disease, asthma, hypertension, stroke, and similar diseases as mentioned above, which are amenable to treatment with potassium channel activating compounds by administration, orally, parenterally, or by aspiration to a patient in need thereof.

What is claimed is:

-1-

A compound of the formula:

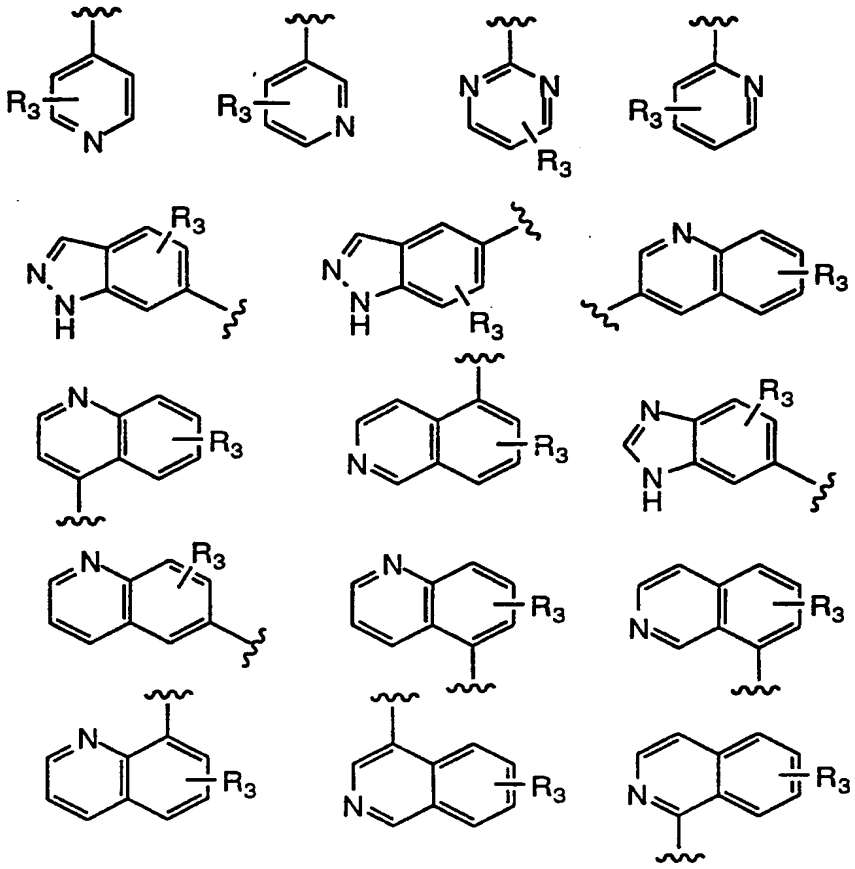


(I)

wherein:

R_1 and R_2 are, independent from each other, hydrogen, C_{1-10} straight chain alkyl, C_{1-10} branched alkyl , or C_{3-10} cyclic or bicyclic alkyl;

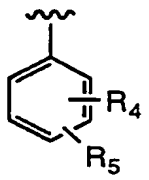
A is is selected from the group consisting of:



wherein:

R3 is hydrogen, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, C1-6 perfluoroalkoxy, amino, C1-6 alkylamino, C2-12 dialkylamino, C1-6 alkylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, nitro, cyano, carboxyl;

or, A is a substituted phenyl group of the following formula:



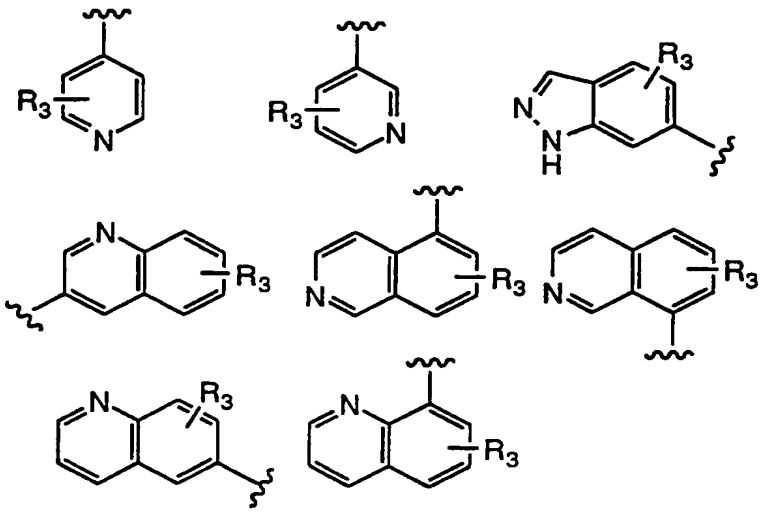
wherein:

R4 and R5, independent from each other, are selected from the following: cyano, nitro, amino, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, C1-6 perfluoroalkoxy, amino, C1-6 alkylamino, C2-12 dialkylamino, sulfamyl, C1-6 alkylsulfonamido, C6-12 arylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, arylcarboxamido containing 7 to 13 carbon atoms, C1-6 alkylsulfonyl, C1-6 perfluoroalkylsulfonyl, C6-12 arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen, with the proviso that R4 and R5 cannot be hydrogen simultaneously;

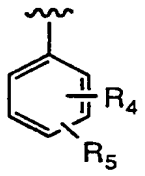
or a pharmaceutically acceptable salt thereof.

-2-

A compound of Claim 1 in which A is selected from the following:



or, A is a substituted phenyl group of the following formula:



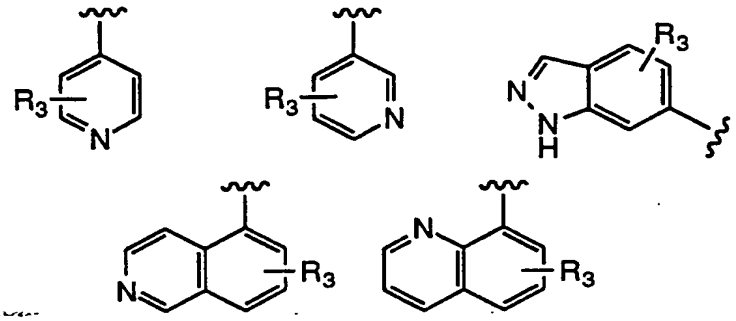
wherein:

R4 and R5, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl,. carboxyl or hydrogen, with the proviso that R4 and R5 cannot be hydrogen simultaneously;

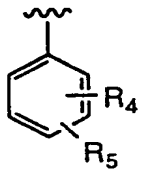
or a pharmaceutically acceptable salt thereof.

-3-

A compound of Claim 1 in which A is selected from the following:



or, A is a substituted phenyl group of the following formula:



wherein:

R_4 and R_5, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl,. carboxyl or hydrogen, with the proviso that R_4 and R_5 cannot both be hydrogen simultaneously;

or a pharmaceutically acceptable salt thereof.

-4-

3-Alkylamino-4-[(substituted phenyl)amino]-cyclobut-3-ene-1,2-dione in which said alkyl group contains 1 to 6 carbon atoms and the phenyl group is substituted by 1 or 2 cyano, nitro, amino, halo or carboxyl group.

-5-

A compound of Claim 1 which is:

3-(pyridin-4-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

(exo)-3-(bicyclo[2.2.1]hept-2-ylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione;

3-(pyridin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

3-(2-methylethylamino)-4-(pyridin-3-ylamino)(cyclobut-3-ene-1,2-dione;

3-dimethylamino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione;

3-amino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione; or

3-tert-butylamino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione.

-6-

A compound of Claim 1 which is:

3-tert-butylamino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione;

3-amino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione;

3-(quinolin-8-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

3-methylamino-4-(quinolin-8-ylamino)-cyclobut-3-ene-1,2-dione;

3-amino-4-(quinolin-8-ylamino)-cyclobut-3-ene-1,2-dione;

3-(quinolin-3-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

3-tert-butylamino-4-(quinolin-3-ylamino)-cyclobut-3-ene-1,2-dione;

3-(quinolin-3-ylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

3-(6-methoxy-quinolin-8-ylamino)-4-(1,2,2-trimethyl-propylamino)-cyclobut-3-ene-1,2-dione;

3-(6-methoxy-quinolin-8-ylamino)-4-methylamino-cyclobut-3-ene-1,2-dione;

3-tert-butylamino-4-(quinolin-6-ylamino)-cyclobut-3-ene-1,2-dione; or

3-(isoquinolin-5-ylamino)-4-methylamino-cyclobut-3-ene-1,2-dione.

-7-

A compound of Claim 1 which is:

3-tert-butylamino-4-(1H-indazol-6-ylamino)-cyclobut-3-ene-1,2-dione;

(exo)-4-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile; or

4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzenesulfonamide.

-8-

A compound of Claim 1 which is 4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzonitrile.

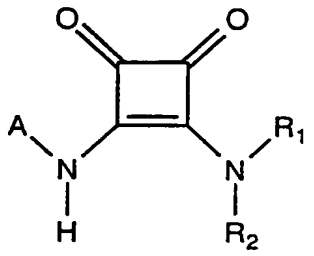
-9-

A compound of Claim 1 which is (+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile.

-10-

A compound of Claim 1 which is (+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-methoxy-benzonitrile.

A method for reducing the adverse effects of smooth muscle contractions which comprises administering, orally or parenterally, to a patient in need thereof, a compound of the formula:

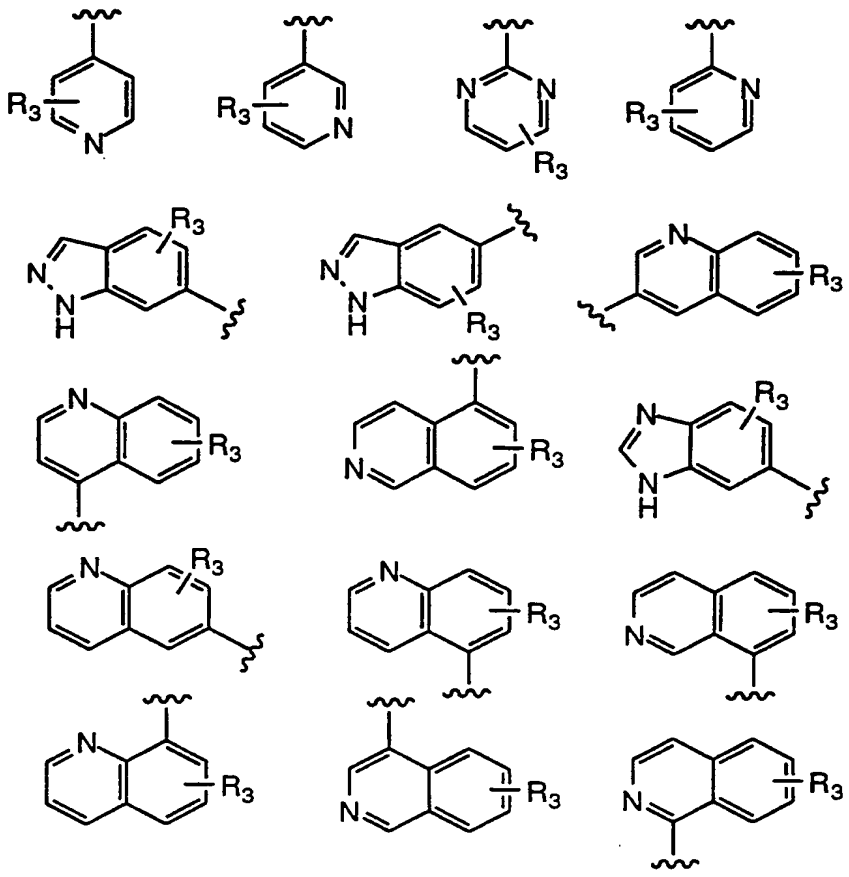


(I)

wherein:

R_1 and R_2 are, independent from each other, hydrogen, C_{1-10} straight chain alkyl, C_{1-10} branched alkyl , or C_{3-10} cyclic or bicyclic alkyl;

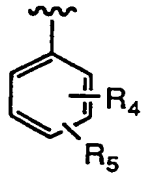
A is is selected from the group consisting of:



wherein:

R3 is hydrogen, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, C1-6 perfluoroalkoxy, amino, C1-6 alkylamino, C2-12 dialkylamino, C1-6 alkylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, nitro, cyano, carboxyl;

or, A is a substituted phenyl group of the following formula:



wherein:

R4 and R5, independent from each other, are selected from the following: cyano, nitro, amino, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, C1-6 perfluoroalkoxy, amino, C1-6 alkylamino, C2-12 dialkylamino, sulfamyl, C1-6 alkylsulfonamido, C6-12 arylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, arylcarboxamido containing 7 to 13 carbon atoms, C1-6 alkylsulfonyl, C1-6 perfluoroalkylsulfonyl, C6-12 arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen, with the proviso that R4 and R5 cannot be hydrogen simultaneously;

or a pharmaceutically acceptable salt thereof.

-12-

The method of Claim 10 in which the smooth muscle adversely contracting causes urinary incontinence.

-13-

The method of Claim 10 in which the smooth muscle adversely contracting causes irritable bowel syndrome.

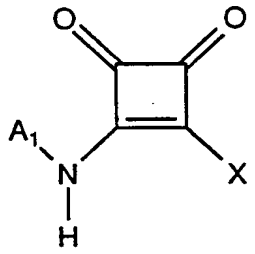
- 38 -

- 14 -

A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 8 in combination or association with a pharmaceutically acceptable carrier.

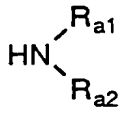
- 15 -

A process for preparation of a compound as claimed in Claim 1, which comprises reaction of a compound having the formula (IIa):



(IIa)

where A_1 is A, as defined in Claim 1, or a group of atoms convertible thereto, and X is a leaving group; with a compound having the formula (IV):



(IV)

wherein R_{a1} and R_{a2} are, respectively, R_1 and R_2, as defined in Claim 1, or a group of atoms convertible thereto and, where appropriate, converting A_1 into A or converting R_{a1} and R_1 or converting R_{a2} into R_2 and, where desired, converting a compound having formula (I) into a pharmaceutically acceptable salt thereof or converting a salt of a compound having formula (I) into a compound having formula (I).

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 94/12561

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/74 A61K31/395 C07D217/02 C07D215/40 C07D215/38
C07D231/56 C07C255/50 C07C311/43

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 426 379 (BEECHAM GROUP PLC) 8 May 1991 cited in the application * page 3-4 * ---	1
Y	EP,A,0 359 537 (BEECHAM GROUP PLC) 21 March 1990 * page 3-4; examples 1-4,6-9,15 * ---	1
Y	US,A,5 011 837 (E.R. SQUIBB & SONS, INC.) 30 April 1991 * complete document * --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 1995	-7. 02. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 94/12561

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.12, 1992, WASHINGTON US pages 2327 - 2340 P.W. MANLEY ET AL. 'Structure-activity studies of potassium channel opening in pinacidil-type cyanoguanidines, ...' * cyanoguanidine compounds * ---	1
P,X	CHEMICAL ABSTRACTS, vol. 121, no. 11, 12 September 1994, Columbus, Ohio, US; abstract no. 133584g, TAKENO,SHUICHI ET AL. 'Preparation of 1,2-diaminocyclobutene-3,4-diones and their pharmaceutical use.' see abstract & JP,A,9 492 915 (SUMITOMO METAL IND.) -----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/US 94/12561

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0426379	08-05-91	AT-T-	115954	15-01-95
		AU-B-	625427	09-07-92
		AU-A-	6554490	02-05-91
		JP-A-	3151374	27-06-91
		US-A-	5147866	15-09-92
EP-A-0359537	21-03-90	AU-A-	4140389	22-03-90
		JP-A-	2134357	23-05-90
		US-A-	5053427	01-10-91
US-A-5011837	30-04-91	US-A-	5278169	11-01-94
		AU-B-	620424	20-02-92
		AU-A-	3895989	15-02-90
		AU-B-	640844	02-09-93
		AU-A-	9007591	13-02-92
		EP-A-	0354553	14-02-90
		JP-A-	2091057	30-03-90
JP-A-9492915		NONE		